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Associations between Periodontal Disease and Alzheimer's Disease: Can brushing you teeth affect Alzheimer's disease?

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1. Abstract

Periodontal disease has recently emerged as an important risk factor for the development of Alzheimer's disease later in life. Although there is still much which is not understood about the specific underlying mechanisms, we know that there is a strong association between the two diseases, which relates to the bacteria involved and the chronic inflammatory states which they share. This review examines the evidence for the co-existence of these diseases and the likely reasons as to why periodontitis may trigger a chain of events which finally presents as the most prevalent dementia worldwide.

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2. Introduction: Alzheimer's disease

Statistics and global burden

Alzheimer's disease (AD) is defined by its pathology, largely the presence of abnormal protein deposits, and is a neurodegenerative disease which usually begins with such symptoms as forgetfulness and ends in severe dementia. The pathology can be summarised in Figure 1. AD is the major cause of dementia worldwide (Alzheimer's Disease International 2016) accounting for between 60 and 80% of dementias. Worldwide, currently more than 46 million people are estimated to have dementia and this is expected to rise to 132 million by 2050, with a global cost reaching \$US 1trillion in the next two years. As the aging population increases the number of people living with AD is set to rise considerably. Although AD is not necessarily an outcome of aging, its incidence approximately doubles every 5 years from the age of 65 years, and the odds of receiving a diagnosis of AD over 85 years of age exceeds 1:3.

Despite the fact that the disease was first discovered over a hundred years ago (Selzmann: English translation, Alzheimer et al. 1995), the drugs available so far are only able to temporarily reduce the symptoms in some people. However, with new understanding of effects of chronic inflammation and the role of the microbiome, novel possibilities for therapy present themselves.

In the brain, aggregates of A β 42 peptides are deposited outside the neurons as 'amyloid plaques'. This toxic peptide has destructive effects on nearby neurons, producing reactive oxygen species (ROS) such as hydrogen peroxide, and sticks to many proteins with high affinity including important cell receptors thereby preventing normal function. A β 42 peptide is produced by most cells including neurons; in AD brain it is spread across the cortical parenchyma and in some subcortical structures. The second characteristic protein aggregation of Alzheimer pathology is that of neurofibrillary tangles (NFT) which are formed inside the neurons. These are composed of peptides cleaved from the protein tau. Tau is a protein which normally enables orderly transport of nutrients and waste in the neurons by stabilising

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microtubules. This pathology, in general, has a predictable trajectory with the NFT accumulation following a proscribed route in the brain, with areas such as the primary motor region classically being spared. The number of NFT correlates well with the stages of dementia; as do amyloid plaques, although less strongly. The greatest risk factor for AD is age; however, an important factor which has been focussed on more recently is that the underlying pathology is likely to be progressing from 15 to 20 years before diagnosis.

Symptoms

The symptoms of the disease can be attributed to the specific areas of the brain affected. The first noticeable symptoms are forgetfulness, attributable to regions such as the hippocampus, and also hyposmia or anosmia, a reduction or loss of sense of smell. Other neuropsychiatric problems include loss of spatial awareness or language function. Neuropsychiatric changes include depression, aggression, wandering and hallucinations. The final stages involve an inability to perform activities of daily living such as washing and feeding. Death usually occurs 8 to 12 years after diagnosis.

A timeline of disease progression

If we consider generally the changes from before the onset of disease up to late stage a theoretical schematic may look like Figure 2.

This relates to changes seen in familial cases of AD and so we cannot be sure that this faithfully reflects changes in sporadic AD, although it does seem to reflect post mortem findings at different stages of the sporadic form of AD. The data are from a prospective, longitudinal study of 128 cases with familial autosomal dominant AD (Bateman et al. 2012) in which assessments of cognition, imaging, blood and cerebrospinal fluid (CSF) levels of tau and A β 42 were obtained. These data indicate that A β 42 deposition, and a reduction in glucose uptake into cells, was seen many years before the expected onset of symptoms. These and other data, which focus on the presumed trigger events, such as amyloid and NFT build up, seem to suggest that efforts should be concentrated on treating patients early, if possible, before any

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symptoms. This has been borne out by the lack of success in treatments so far. This narrows our options.

One possibility is to test for non-intrusive markers of pathology for everyone, preferably in those less than 60 years of age, or another to 'treat' everyone regardless, such as currently occurs with vaccines for measles. However, especially in the face of the prevailing financial climate, a third option of prevention seems commendable. A number of studies have shown that AD is amenable to lifestyle changes and may relate to poor oral health. Stabilisation of active periodontal disease and subsequent reduction in oral pathogen load, may possibly lead to a large enough reduction in risk of having dementia to delay its onset beyond our lifetime.

Age, inflammation and the adaptive and innate immune systems

Many studies have shown it is possible to have numerous amyloid plaques in the brain without cognitive decline (Price & Morris 1999, Aizenstein et al. 2008, Hulette et al. 1998, Katzman et al. 1988, Esparza et al. 2013). Rather than assuming these people all to be 'pre-clinical' we might consider the disease in separate phases such that in an initial stage there may be a trigger causing production of A β and tau proteins but later in a cellular phase, the main driver of pathology becomes inflammation (Karran & De Strooper 2016). If it is the inflammatory changes which stimulate the actual process of neurological damage, bearing in mind that in Figure 2 we see no cognitive damage until after 20 years of A β 42 deposition in the parenchyma, then reducing the inflammatory drive may slow or prevent cognitive decline. Amyloid (A β) production is a part of our normal response to acute injury and it is a possibility that the amyloid plaques present in the brains of non-demented individuals are the result of a successful attempt by the brain to deal with an acute insult from microbial pathogens. If we view the whole disease process in this way we can begin to think about (i) prevention from an early age and (ii) therapy even after the symptoms have manifested.

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There is, in fact, much evidence to show that chronic inflammation is a major driver of AD (Weksler et al. 2005, Heneka et al. 2015, Heppner et al. 2015, Marsh et al. 2016). The sources of sustained inflammation may be manifold; however we have some indications as to the principal promoters. The first of these is age. More than 95% of those with AD are over 65 years; 81% are age 75 or older. Our health depends upon an active immune system to protect us from pathogens. As we age, in many cases the adaptive immune system which deal with pathogens in a controlled and enduring manner gradually weakens (Weksler et al. 2005, Weinberger et al. 2008, Castelo-Branco & Soveral 2014, Simon et al. 2015). This leaves the innate immune system as our principal champion of defence; this is rapid but less controlled and may result in excessive production of cytokines or other anti-bacterials which may also damage neurons. With age then, we become more vulnerable to the effects of any prolonged and excessive response to invading microorganisms or other triggers, not only from the microbes themselves but from our own excessive response to them.

Due to the lack of free movement of antibodies across the blood-brain-barrier (BBB) into the brain, microglial cells are the primary immune cells of the brain and have been identified as being central to inflammatory states in many diseases (Cherry et al. 2014, da Fonseca et al. 2014, Holtman et al. 2015). The microglial phenotype is modified by infection by bacteria or other microbial pathogens, and microglial cells become 'primed' during aging and in pathological inflammatory situations (Holtman et al. 2015). Microglia can exist in an activated classical pro-inflammatory state (M1) and an 'alternatively activated' (M2) supportive, anti-inflammatory state. Enhanced phagocytic activity of microglia is likely to be supportive of a degenerating brain in the short term. However, prolonged or dysregulated microglial activation, especially in the context of additional inflammatory events, may result in impaired phagocytosis with increased release of reactive oxygen species (ROS) or cytokines which may exacerbate neuronal damage.

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In the vicinity of bacteria or amyloid plaques, microglia produce antibacterial proteins or cytokines in order to eliminate invading pathogens.

3. The proposed mechanism of association between periodontitis and Alzheimer's disease.

Following from the understanding that a major driver of AD pathology involves chronic brain inflammation we may ask the question as to how this arises. Recent evidence suggests that A β 42 itself may be an antibacterial (Soscia et al. 2010, Kamer et al. 2016) and it is probably part of our innate immune system. Therefore A β 42 may act to kill bacteria, but also its increased production and deposition may result in microglial activation and an upregulation of inflammation which inadvertently sustains a chronic activation of primed microglia which initiates a cycle of inflammatory upregulation. If we assume that one of the possible triggers of chronic inflammation is bacteria the where does this originate?

From the oral and nasal cavities to the brain

Infections may occur anywhere within the body producing first acute and then chronic infection and inflammation. However, the result of this is usually heat and pain, alerting the host to the site of infection. The mouth is a privileged site in terms of immune response (Novak et al. 2008). Despite the fact that there is a large number and diversity of bacteria within the oral cavity and that the mouth is constantly in contact with allergens, there is not the expected requisite number of inflammatory episodes and this has resulted in the suggestion that the mouth is an immune tolerant site (Novak et al. 2008). In reality this leads to a situation where low level chronic infection, such as periodontitis, may occur over decades without any noticeable level of pain or pyrexia. We therefore suggest that periodontitis provides an ideal driver of inflammation in the brain, able to produce cytokine secretion into the bloodstream, and also situated close enough to the olfactory bulb and tract which allows a direct passage into the cortical parenchyma.

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The latter would also explain the presence of Alzheimer pathology in the olfactory bulb (Ohm & Braak 1987, Jellinger & Attems 2005, Franks et al. 2015) which is associated the common early loss of sense of smell which is associated with the progression of pathology (Doty et al. 2003, Doty & Kamath 2014) and with clinical dementia (Attems et al. 2005, Attems & Jellinger 2006). This has been recognised as a potential marker for diagnosis (Atanasova et al. 2008, Djordjevic et al. 2008). The association between periodontitis and AD is further reviewed (Cerajewska et al. 2015, Shoemark & Allen 2015).

Evidence: Epidemiology, genetics and scientific research

Epidemiology

A number of epidemiological studies suggest that poor gum health is a risk factor for AD. A study using data from 'The Swedish Twin Registry', in which over 3,000 monozygotic twins were assessed for risks for dementia (Gatz et al. 2006) found it fourfold more likely that the twin with AD had poorer oral health, and tooth loss before age 35 years, compared with the sibling without dementia. Poor oral health was therefore a significant risk factor. In accord with this, in 2007 a 10 year longitudinal study of dental records of nuns (the Milwaukee Nun Study) of between 75 and 98 years old showed that those with the fewest teeth, lost due to periodontal disease, had the highest risk of dementia (Stein et al. 2007). In 2012, an 18 year longitudinal study of 5468 normal adults (average 81 years) showed that brushing teeth regularly lowered the risk of AD. Those who did not brush regularly had up to a 65% increased risk of dementia (Paganini-Hill et al. 2012). Recently a small observational study, in which 60 AD patients with and without periodontitis were cognitively assessed and inflammatory markers measured in the blood, showed that after six months there was a six fold increase in the rate of cognitive decline in those with periodontitis compared to those without (Ide et al. 2016). This would be a remarkable finding and needs to be confirmed by further studies.

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Post mortem studies in Alzheimer brain

Some bacterial infections of the brain, such as seen with bacterial meningitis caused by *Neisseria meningitides*, have severe acute reactions. Other bacteria are able to invade brain tissue without causing such an immediately obvious effect. Diverse bacterial species have been identified in human brain tissue and have been found at higher levels in Alzheimer brain. Early reports by Judith Miklossy showed obligate oral based anaerobes such as spirochetes, were present in blood and CSF from Alzheimer patients but not in age-matched controls (Miklossy 1993) and the literature data for the evidence of oral spirochetes in AD brain has been reviewed with the reported presence of spirochetes in over 90% of AD brains (Miklossy 2011). Additionally, spirochete oral pathogens including *Borrelia burgdorferi* and various Treponemas have been detected at much greater levels than in controls (Riviere et al. 2002, Branton et al. 2013). Recently, A β was shown to be a major component of spirochetal biofilms within amyloid plaques in AD brain tissue and it is suggested that bacterial amyloid is a constituent of AD plaques and may contribute to uncontrolled inflammatory drive (Miklossy 2016). Furthermore, elevated plasma levels of antibodies to the oral bacteria *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia* and *Porphyromonas gingivalis* were found in AD patients compared with controls (Kamer et al. 2009). Additionally, in a longitudinal study in cognitively normal people, higher baseline serum antibody levels, specific for the oral anaerobes *Fusobacterium nucleatum* and *Prevotella intermedia*, were shown to correlate a decade later with cognitive deficits (Sparks Stein et al. 2012).

Bacterial infiltration into the brain is likely to result in inflammation and secretion of pro-inflammatory cytokines. For example, TNF α CSF levels in Alzheimer patients were reported as 25-fold that of controls (Tarkowski et al. 1999). Cellular stress and microbial infections elicit inflammatory reactions; in response to this inflammasomes assemble and a cascade of further secreted cytokines is initiated adding to subsequent pathological processes (Singhrao et al. 2015). The major component of the outer membrane of gram-negative bacteria is lipopolysaccharide (LPS), and LPS from the oral anaerobe *P. gingivalis* has

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been detected in the brains of AD patients, but not in control brain tissue (Poole et al. 2013). LPS binds the microglial cell receptor TLR4 and increases inflammation via inflammasome-induced cytokines. Interestingly it has been shown that the TLR4 content in peripheral blood mononuclear cells was increased fourfold in 60 late-onset AD patients as compared to 60 healthy controls with a negative correlation between TLR4 levels and cognitive score (Zhang et al. 2012).

Oral periodontal bacteria implicated in Alzheimer's disease

More than 600 species of oral bacteria have been identified in periodontal pockets. 16S rRNA gene sequences of these bacteria are collected in the Human Oral Microbiome Database (HOMD; www.homd.org) and have been further examined in detail (Chen et al. 2010, Dewhirst et al. 2010). Figure 5 shows some of the most pathogenic of these bacteria and their social groupings.

With periodontitis a shift in oral population is seen from predominantly aerobic gram positive bacteria such as streptococci to favour gram-negative anaerobic bacteria, usually rods not cocci, including *P. gingivalis*, *P. intermedia* and *Treponema denticola*. There is evidence that bacterial communities associated with periodontitis are 'inflammo-philic' and are able to use nutrients produced from the breakdown products from gum tissue and bone. In accord with this, anti-inflammatories are able to reduce the bacterial load and prevent loss of bone (Hajishengallis & Sahingur 2014).

Genetic links between AD, inflammation and bone health.

The inflammatory component of AD has long been identified and its relevance noted (Lue et al. 1996, McGeer & McGeer 1999). However, for many reasons, including the fact that anti-inflammatory drugs were not generally successful, the concept was not fully explored. However, more recently genome-wide association studies have brought new interest which, when examined in very large cohorts suggest that genes involved in processes of inflammation are risk factors for AD. Seven genes in particular are of

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interest here: APOE, TREM2, SHIP1, CD33, CR1, and ABCA7 due to their ability to activate microglia. (Malik et al. 2015). Microglia can be neuroprotective or neurotoxic, or both, depending on other influences.

Intimately associated with bone resorption is the loss of vitamin D, and a number of studies relate lower serum levels of vitamin D with extent of periodontitis. Chronic periodontitis is caused by increased resorption of the alveolar bone, which supports the teeth, and presents with infection and inflammation, so unsurprisingly, genetic polymorphisms (in the vitamin D receptor have been associated with periodontitis. Less obvious perhaps is a link between vitamin D and AD. However, Vitamin D elicits neuronal protection by a number of mechanisms including reduction of inflammation, partly by suppressing pro-inflammatory cytokines such as TNF- α , and increased removal of A β 42 (Kalueff & Tuohimaa 2007, Annweiler et al. 2011); and various studies do show associations of specific vitamin D receptor polymorphisms with an increased risk of onset of AD (Gezen-Ak et al. 2007) particularly in older people over 75 years (Lehmann et al. 2011).

4. Proposed benefits of periodontal health/treatment for the evaluated disease

The link between periodontal disease and a number of chronic systemic diseases and conditions is now well established. Over the last decade in particular, a large body of research work has demonstrated periodontitis as an independent risk factor for many systemic conditions including atherosclerosis and stroke (Dietrich et al. 2013), coronary heart disease (Schenkein & Loos 2013), adverse pregnancy outcomes (Ide & Papapanou 2013) and diabetes (Borgnakke et al. 2013). Further to these associations, there is now emerging evidence for links between periodontitis with nosocomial pulmonary infections, pancreatic cancer, rheumatoid arthritis, and as shown in this paper, AD.

As indicated earlier in this article, changes in the brain associated with AD have been shown to precede the diagnosis by up to 20 years (Bateman et al. 2012) and suggest that patients should be treated early before the onset of symptoms. The importance of periodontal therapy in periodontal patients, therefore

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may extend beyond the treatment of the immediately apparent oral problem and impart longer term benefit in reducing their risk of developing AD. For those already suffering with AD, the evidence suggests that periodontal treatment may be able to slow disease progression.

As well as being a risk factor for AD, periodontal disease is also frequently a consequence. Depending on the stage of AD, oral hygiene can be significantly compromised, particularly in the advanced stages. The cognitive processes of learning are affected and attention of the individual is often compromised with the memory being progressively damaged. This means the individual forgets to carry out the brushing process and when brushing can't remember how to brush or for how long. Motor skills are also poor (Ghezzi & Ship 2000) and as the dementia advances, more daily activities are disrupted, often resulting in poor or no toothbrushing. In a susceptible individual this will lead to gingivitis, periodontal disease, bad breath and tooth loss. The final outcomes of periodontal disease are progressively severe destruction of the tooth supporting apparatus, tooth loss and masticatory dysfunction.

The benefits of treating periodontitis with good self directed/ carer led oral hygiene and regular supportive periodontal therapy are multiple and of high impact for AD individuals. Often oral health is not a priority treatment for this sector of society and a recent systematic review found that older people with dementia had worse oral health than older people without dementia (Delwel et al. 2016). Periodontal treatment greatly increases the outcome of maintaining the dentition and stabilizing periodontal disease improving chewing function, quality of life with social interaction and wellness (Cicciu et al. 2013), with lack of treatment often resulting in oral disability accompanied with poor quality of life, poor nutritional status and compromised speech and aesthetics (Chapple 2014), irrespective of the possible negative effects on AD progression.

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5. Summary

The suggested association between periodontitis and Alzheimer's disease is explained in Figure 6. Oral bacteria associated with periodontitis chronically secrete pro-inflammatory cytokines and LPS (bacterial lipopolysaccharides or endotoxins), which travel into the bloodstream, initiating microglial activation in the brain with subsequent chronic inflammation. Bacteria may also enter the brain via the olfactory tract. Microglial cells in the brain are activated via these mechanisms and by A β activation. The overall result is chronic brain inflammation with subsequent neuronal death over decades.

6. Conclusions

We have provided strong evidence to suggest that periodontitis, as a chronic infection, is a likely candidate as an initiator of the cellular, inflammatory phase of AD. By providing stimulus such as LPS and by producing enzymes capable of tissue and bone dissolution, the periodontal bacteria are able to provoke a potentially destructive host response resulting in cytokine infiltration with subsequent microglial activation via peripheral circulation into the brain. They also have close access to the areas of the brain affected in AD, and since there is evidence of their presence in Alzheimer brain tissue then it is likely that they also penetrate via the olfactory route into the brain. We suggest that treatment for periodontitis should be of primary importance along with an effort to encourage oral hygiene via brushing and attention to the right diet from a young age.

7. Implications for action: for the dentist and for the population.

For any patient, continuity of care is a valuable attribute for successful dental management. With those living with AD the benefit of long term rapport between the dental team and patient/family plays a vital role in the patient-centred approach to treatment. Treatment planning needs to be mindful of the stage of cognitive impairment and working well with the family and carers is crucial to understanding limitations and optimize treatment outcomes. Rigorous oral hygiene measures should be instigated at both home

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and in the surgery from the outset of diagnosis. In the early stages of dementia every effort must be made to render the patient dentally fit with restorations of high quality and relatively low maintenance (McNamara et al. 2014). The dental care plan needs to take into account that, as dementia progresses, the person will be less able to express their needs or wishes, understand and explain oral symptoms such as pain, make decisions and indeed give informed consent (McNamara et al. 2014).

The prevalence of severe periodontitis in 2014 was 11%, the global burden of periodontal disease being the sixth most chronic disease of mankind (Kassebaum et al. 2014). These figures are estimated to increase in the future due to increasing life expectancy and a substantial decrease in the prevalence of tooth loss throughout the world from 1990 to 2010 (Kassebaum et al. 2014), although frighteningly, the vast majority of periodontitis cases are totally preventable with good oral care. Figures for comparable years showed there were 46.8 million people worldwide living with dementia in 2015, with numbers estimated to double every 20 years, to 74.7 million in 2030 and 131.5 million in 2050. These new estimates being 12-13% higher than those made for the World Alzheimer Report 2009. Taken individually both AD and periodontal disease have severe consequences for the world population, however if periodontal diseases could be controlled by excellent oral hygiene and regular supportive dental care, teeth could be maintained with all the advantages described above and possibly AD may be slowed in the early stages with immense benefit for all. Dental and medical healthcare professionals and policy makers need to raise the profile of periodontal disease to ensure the world population is aware of the benefits that can be achieved by improving oral health particularly in our elders, and further, committed to delivering and supporting this care across all boundaries on a lifelong basis for a better life.

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Neuropathology

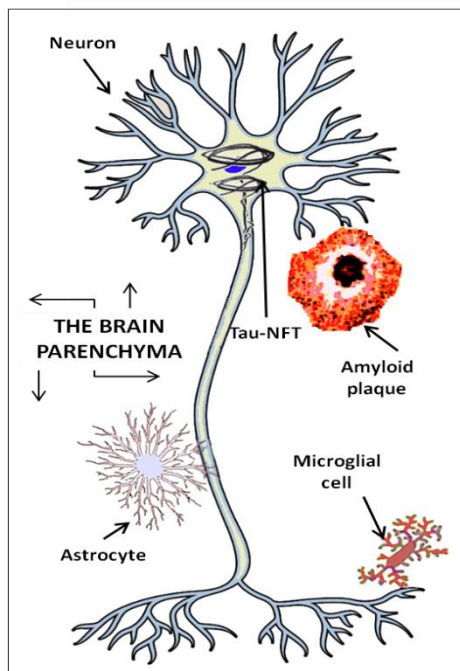


Figure 1. Schematic of cell types in the brain parenchyma and the neuropathology associated with Alzheimer's disease.

The two major characteristic markers of pathology in the brain are amyloid plaques and neurofibrillary tangles (NFT). Amyloid plaques are composed mainly of aggregates of the A β 42 peptide (42 amino acids long), which are deposited outside the neurons in the brain parenchyma i.e. surrounding tissue. NFT accumulate inside the neurons, and are comprised mainly of peptides from the protein tau, which have an unusually high level of phosphate groups on them. Glial cells are also shown: a microglial cell and an astrocyte, which support the neurons but under certain circumstances can be involved in neuronal damage.

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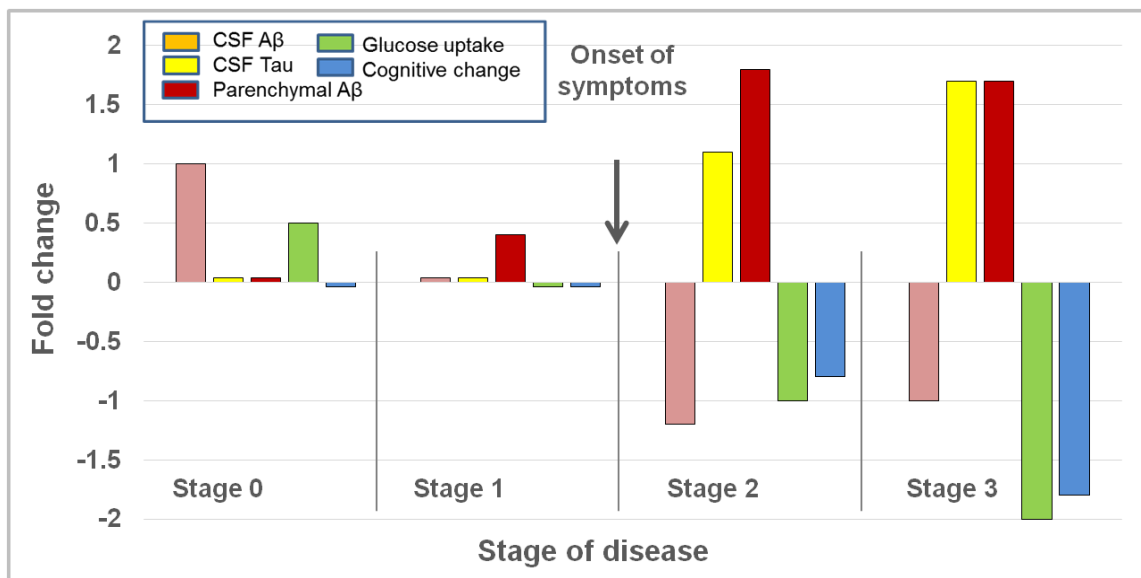


Figure 2. Changes in brain function from pre-disease to late stage familial Alzheimer's.

Adapted from Bateman et al. 2012 (Bateman et al. 2012) Longitudinal data, from before onset of symptoms, obtained from people with known AD dominant mutations. This bar chart shows reductions in Aβ42 (orange bars) in cerebrospinal fluid (CSF) over time, commensurate with increases in parenchymal deposition of Aβ42 (red bars) (measured by positron-emission tomography with Pittsburgh compound B (PIB) which binds amyloid) into plaques; a reduced glucose uptake (green bars; measured by fluorodeoxyglucose (FDG)), and an increase in tau into the CSF (yellow bars) which is probably related to disintegration of the neurons. Stage 0 is before the start of the neuropathological process, stage 1 relates to data at 20 years before symptoms, stage 2 is at onset of symptoms and stage 3 is 10 years after diagnosis.

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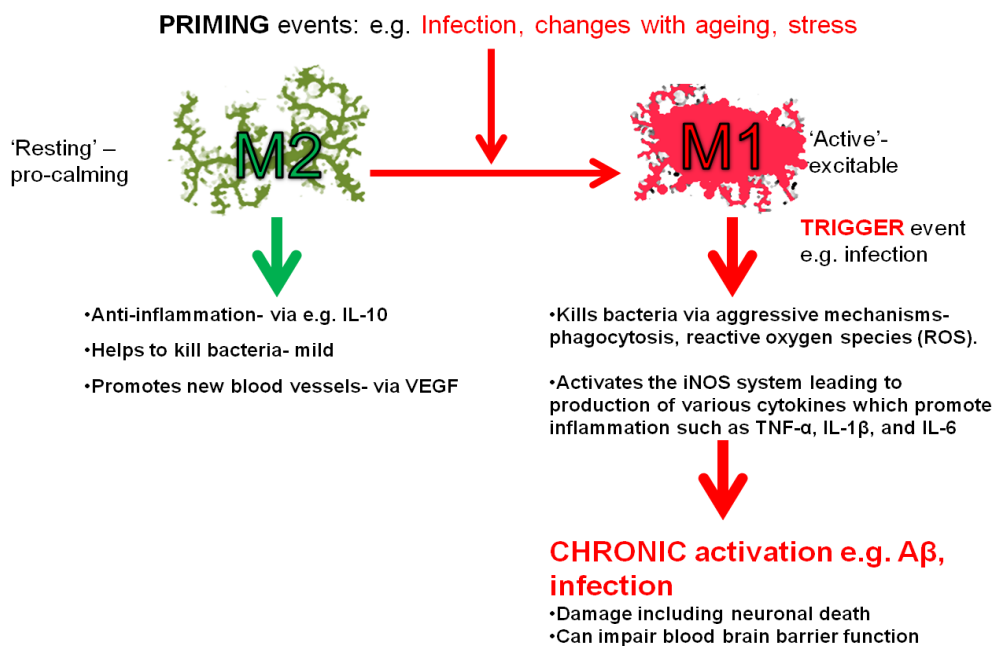


Figure 3. How microglia may cause chronic inflammation.

Microglial cells are a major part of the brain's immune system, and depending on circumstances move between a so called 'resting' state (M2) and an 'activated' state (M1). Normally the M2 microglia keep the brain in a balanced state, help to control any minor infections, reduce inflammation and also when necessary promote sprouting of blood vessels to help with the flow of nutrients and oxygen. Acute events, such as infection or stress, can alert these cells to change into a more active state. After the event is dealt with they return to a supportive M1 state. However, if provoked chronically, this can lead to a state of hyper-inflammation in which neuronal cell death may occur.

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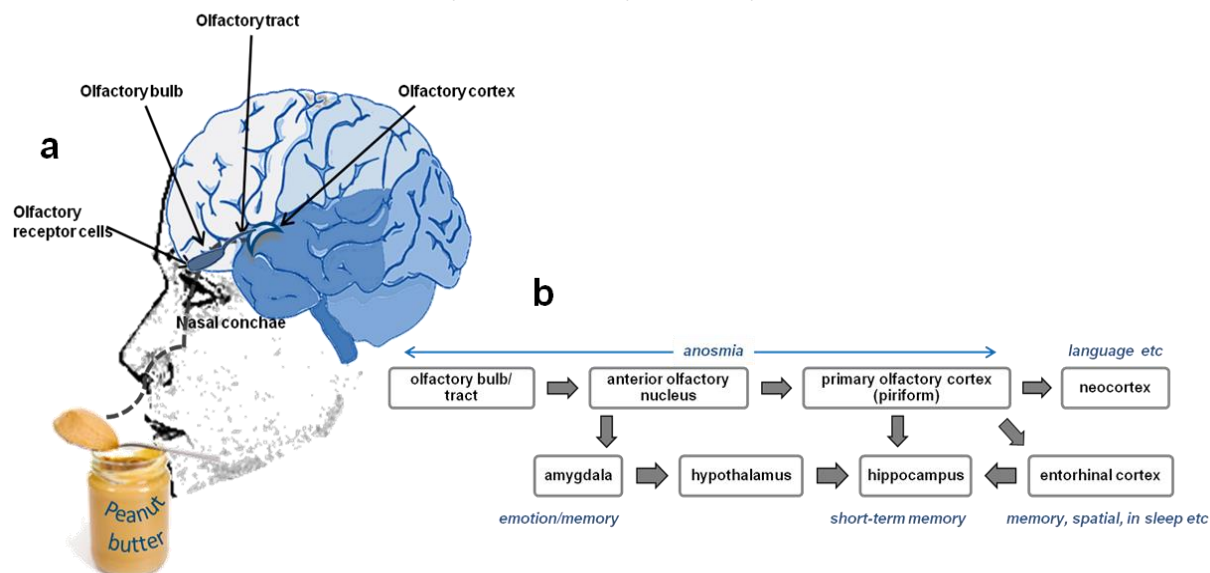


Figure 4 A pathway from the oral/nasal cavities to the cortical areas of the brain – a possible route by which pathogens may reach the brain. (Atanasova et al. 2008) The olfactory tract is a likely route for the spread of pathogens such as bacteria and viruses into the brain. Ability to perceive peanut butter may be used as a part of a 'smell test' for diagnosis of AD. (Price & Morris 1999) The systems which are affected such as the olfactory tract, which contains the classical Alzheimer pathology.

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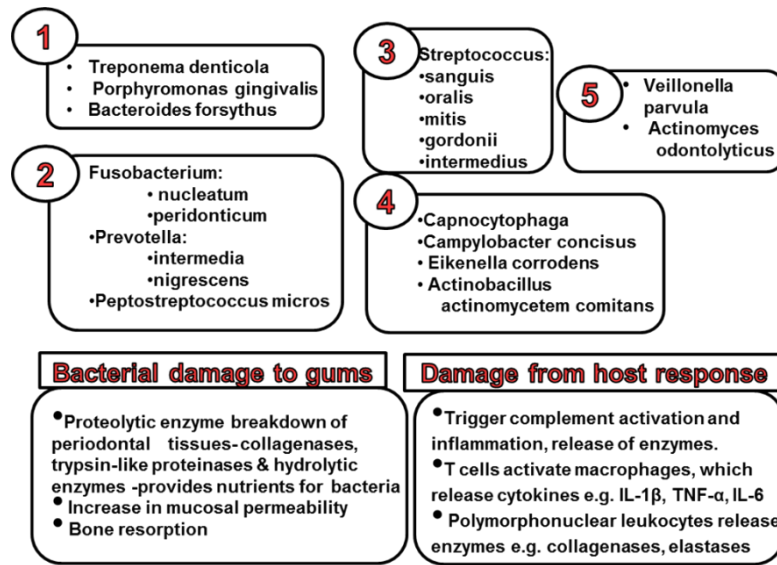


Fig 5 Some of the oral bacteria implicated in dementia and their affiliations. Adapted from (Socransky et al. 1998, Hasan & Palmer 2014) Social groupings of bacterial species have been described. It has been suggested that growth factors or other nutrients may be produced by some that are required by others. Group 1 is most strongly associated with clinical measures of periodontal disease especially for pocket depth and bleeding on probing.

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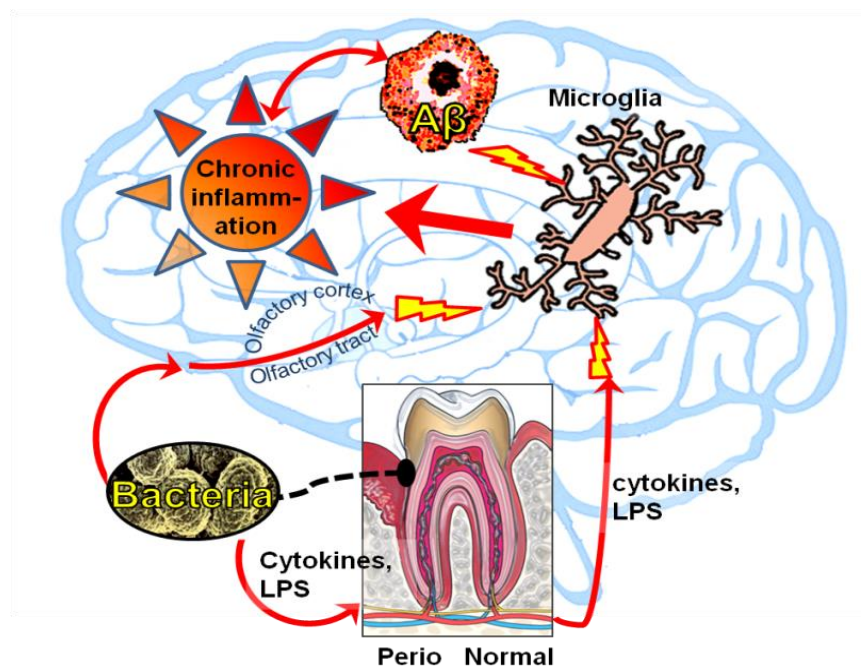


Figure 6. Suggested association between periodontitis and Alzheimer's disease.

Oral bacteria associated with periodontitis chronically secrete pro-inflammatory cytokines and LPS (bacterial lipopolysaccharides or endotoxins) which travel into the bloodstream, initiating microglial activation in the brain with subsequent chronic inflammation. Bacteria may also enter the brain via the olfactory tract. Microglial cells in the brain are activated via these mechanisms and by A β activation. The overall result is chronic brain inflammation with subsequent neuronal death over decades.